REMARKS

Reconsideration of the present application is requested in view of the foregoing amendments and the following remarks.

I. Examiner Interview

The Applicants thank Examiner Goldberg for participating in a telephone interview with the Applicants' representative, M. Scott McBride, on October 23, 2008. The participants discussed the outstanding rejection for lack of enablement and whether the rejection might be overcome by amending the claims to recite an additional eight (8) genes that are present in Table 3 of the Grant Proposal of the Levenson Declaration. The Applicants' representative indicated that the claims would be amended accordingly and submitted with a Request for Continued Examination.

II. Amendments to the Claims

Prior to entry of the foregoing amendment, claims 1-5, 12-14, 24-28, 31, 33, and 34 were pending.

Claims 3, 4, 5, 12-14, 24, 33, and 34 are requested to be cancelled without disclaimer or prejudice to further prosecution on the merits.

Claims 35 and 36 are requested to be added.

Claim 1 currently is amended to recite "contacting said digested genomic DNA with gene specific primers, wherein said gene specific primers are configured to hybridize to said genomic DNA and amplify different promoters from different genes including DAPK, FAS, MCT1, p16, PAX5, THBS, TRANCE, and VHL." New claims 35 and 36 similarly recite "contacting said digested genomic DNA with gene specific primers, wherein said gene specific primers are configured to hybridize to said genomic DNA and amplify different promoters from different genes including DAPK, FAS, MCT1, p16, PAX5, THBS, TRANCE, and VHL."

In the Office Action dated June 17, 2008, the Examiner asserted that the gene "THBS" was not included within the list of genes in Figures 2 and 3. The Applicants respectfully disagree. The gene "THBS" is contemplated in the specification and its methylation status was in fact analyzed as indicated in Figure 3.

Gene	SRBC	SYK	TES	THBS	TMS1	TRANCE	uPA	VHL
MDA	UM	M	UM	UM	M	M	UM	UM
MCF-7	M	M	M	UM	M	M	UM	UM
T47D	M	UM	M	UM	M	UM	M	UM
T1	M	M	M	M	M	M	ND	M
N1	M	M	M	UM	M	M	ND	M

(*See* Figure 3, Bottom Table, column 4.)

New claim 35 differs from amended claim 1 in that new claim 35 recites "[a] method for characterizing ductal breast cancer in a subject," rather than "[a] method for diagnosing breast cancer in a subject." New claim 36 differs from amended claim 1 in that new claim 36 recites "[a] method," rather than "[a] method for diagnosing breast cancer in a subject." These limitations are supported in the original specification and claims. In particular, support for "ductal carcinoma" is provided in the original specification at page 7, lines 18-20, stating ("[a]s used herein, the term "sub-type of cancer" refers to different types of cancer that effect the same organ (ductal cancer, lobular cancer, and inflammatory breast cancer are sub-types of breast cancer").

These amendments do not introduce new matter and otherwise are proper. For these reasons, entry thereof is requested. After entry of the amendments, claims 1, 2, 25-28, 31, 35, and 36 are pending.

III. Claim Objection with Respect to Dependency of Claim 34

Claim 34 was rejected for being in improper dependent form. Claim 34 has been cancelled obviating the rejection.

IV. New Matter Rejection with Respect to Recitation of the Gene "THBS"

Claims 4 and 24 were rejected allegedly for reciting new matter with respect to the term "THBS." The Examiner contends that the specification does not describe or discuss the "THBS" gene and fails to include the "THBS" gene within the list presented in Figures 2 or 3. The Applicants respectfully disagree as discussed above.

For these reasons, withdrawal of the objection is requested.

V. Claim Rejection - Scope of Enablement

The Examiner has reviewed the Levenson Declaration submitted on April 29, 2008 but finds that the Levenson Declaration does not disclose a composite biomarker for detecting breast cancer. Furthermore, the Examiner contends that the scope of the claims is not commensurate with the results presented in the Declaration. The Applicants respectfully traverse the rejection in view of the foregoing claim amendments, in view of the Leven Declaration, and for the following reasons.

The claims have been amended to recite eight genes including DAPK (otherwise known in the art as "death associated protein kinase"), FAS (otherwise known in the art as "apoptosis stimulating fragment"), MCT1 (otherwise known in the art as the "multiple copies of T-cell malignancy" gene and which is synonymous with "MCTS1"), p16 (which encodes a ~16 kDa protein and is otherwise known in the art as "CDKN2A"), PAX5 (otherwise known in the art as "paired box protein 5"), THBS (otherwise known in the art as "thrombospondin"), TRANCE (otherwise known in the art as "tumor necrosis factor ligand superfamily member 11" or "TNFSF11"), and VHL (otherwise known in the art as "Von Hippel-Lindau disease tumor suppressor"). Copies of the Swiss-Prot entries for these genes are submitted herewith as part of an information disclosure statement. The Swiss-Prot entries list recognized synonyms for these genes and the encoded proteins.

The Levenson Declaration describes a Grant Proposal and in particular Table 3 in which ten (10) genes are utilized as a biomarker for ductal carcinoma in situ (DCIS), which is a Stage 0 cancer and is the earliest form of breast cancer.

Table 3. Genes of the biomarker and their methylation in plasma of DCIS patients and healthy controls.

Gene	DCIS	Normal
DAPK1	89.3%	51.9%
FAS	82.8%	33.3%
MCTS1	66.7%	28.6%
CDKN2A	74.1%	35.3%
PAX5	75.0%	40.0%
PGK1	78.6%	37.5%
RPL15	53.8%	13.0%
THBS	82.1%	36.8%
TNFSF11	72.7%	30.0%
VHL	91.3%	25.0%

The ten (10) genes in Table 3 were utilized to diagnose DCIS in plasma from twenty-nine (29) patients with a sensitivity of 84% and a specificity of 80%.

Table 4. DCIS detection in plasma.

	DCIS	Normal
pDCIS	84.48%	19.87%
pNormal	15.52%	80.13%

The present claims have been amended to recite eight (8) of the ten (10) genes listed in Table 3, including DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, and VHL. The Applicants respectfully submit that the methylation status of these eight (8) genes in plasma can be utilized to practice the claimed methods as evidenced by the Levenson Declaration. In particular, Table 3 shows that:

DAPK exhibits methylation in 89.3% of DCIS patient samples versus 51.9% of normal patient samples;

FAS exhibits methylation in 82.8% of DCIS patient samples versus 33.3% of normal patient samples;

MCTS exhibits methylation in 66.7% of DCIS patient samples versus 28.6% of normal patient samples;

P16 (*i.e.*, CDKN2A) exhibits methylation in 74.1% of DCIS patient samples versus 35.3% of normal patient samples;

PAX5 exhibits methylation in 75.0% of DCIS patient samples versus 40.0% of normal patient samples;

THBS exhibits methylation in 82.1% of DCIS patient samples versus 36.8% of normal patient samples;

TRANCE (*i.e.*, TNFSF11) exhibits methylation in 72.7% of DCIS patient samples versus 30.0% of normal patient samples; and

VHL exhibits methylation in 91.3% of DCIS patient samples versus 25.0% of normal patient samples.

Therefore, any one of these listed genes exhibits differential methylation in DCIS patient samples versus normal patient samples. The claims require assessing the methylation status of each of the eight (8) recited genes.

Furthermore, the Applicants respectfully submit that the methylation status of these eight (8) genes in plasma can be utilized to practice the claimed methods as evidenced by knowledge in the art. In particular, the Applicants submit that the methylation status of p16 (*i.e.*, CDKN2A) in plasma is recognized in the art as being diagnostic for breast cancer. (*See, e.g.,* Silva *et al.*, "Aberrant DNA methylation of the p16 INK4a gene in plasma DNA of breast cancer patients," Brit. J. of Cancer

(1999) 80(8), 1262-1264; Silva *et al.*, "Presence of Tumor DNA in Plasma of Breast Cancer Patients: Clinicopathological Correlations," Cancer. Res. 59, 3251-3256, July 1, 1999; and Silva *et al.*, "Persistence of Tumor DNA in Plasma of Breast Cancer Patients After Masectomy," Annals of Surgical Oncology, 9(1):71-76 (2002)). Therefore, the methylation status of p16 in plasma alone is recognized as being diagnostic of breast cancer. The claims go further and require assessing the methylation status of p16 and seven (7) other genes each of which exhibits differential methylation in DCIS patient samples versus normal patient samples. The Applicants ask the Examiner to reconsider whether the claims are enabled in view of the Levenson Declaration and in view of knowledge in the art.

Furthermore, claim 35 recites "[a] method for characterizing ductal breast cancer in a subject," and claim 36 recites "[a] method." The Applicants ask the Examiner to reconsider whether these claims are enabled in view of the Levenson Declaration and in view of knowledge in the art.

The Examiner also contends that the scope of the claims is not reasonably correlated with the results provided in the Levenson Declaration. The Applicants ask the Examiner to reconsider this contention in view of the foregoing claim amendments where the claims have been amended to recite eight (8) of the ten (10) genes disclosed in Table 3 of the Grant Proposal.

For these reasons, reconsideration and withdrawal of the rejection for lack of enablement are requested.

VI. Claim Rejections – Indefiniteness of Claims 3-5 and 12-14

Claims 3-5 and 12-14 were rejected for alleged indefiniteness where claim 3 requires a plasma sample but recites a "biological sample" in step (a). Claims 3-5 and 12-14 have been cancelled obviating the rejection.

VII. Conclusion

The Applicants have attempted in earnest to respond to the outstanding Office Action. Allowance of the pending claims is requested. If the Examiner believes that a conference will facilitate prosecution of the application, the Examiner is requested to contact Applicants' representative below.

Respectfully submitted,

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